AF

Docket No.: PF-0525 USN
Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1647

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By: _____ Printed: Lisa McDill

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title: HUMAN SOCS PROTEINS

Serial No.: 09/701,232 Filing Date: July 5, 2001

Examiner: Hamud, F. Group Art Unit: 1647

BOX AF

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TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard;
2. Brief on Appeal, including Appendix (58 pp., in triplicate);
3. Declaration of John C. Rockett, Under 37 C.F.R. §1.132, with Exhibits A - Q (in triplicate);
4. Second Declaration of Tod Bedilion, Under 37 C.F.R. §1.132 (in triplicate);
5. Declaration of Vishwanath R. Iyer, Under 37 C.F.R. §1.132, with Exhibits A - E (in triplicate); and
6. Nineteen (19) References (1 - 19) (in triplicate).

The fee has been calculated as shown below.

___ No additional Fee is required.

X Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c): $ 330.00

X Please charge Deposit Account No. **09-0108** in the amount of : $ **330.00**

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

INCYTE CORPORATION

Date: February 19, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Lal et al.

Title: HUMAN SOCS PROTEINS

Serial No.: 09/701,232 Filing Date: July 5, 2001

Examiner: Hamud, F. Group Art Unit: 1647

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed December 16, 2003; and received by the USPTO on December 19, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the **$ 330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting Claims 21-29, 31-32, and 36-37 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Genomics, Inc. (now Incyte Corporation) (Reel 012027, Frame 0086) which is the real party in interest herein.

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(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: Claims 21-29, 31-32, and 36-37

Claims allowed: (none)

Claims canceled: Claims 1-20

Claims withdrawn: Claims 30, 33-35, and 38-40

Claims on Appeal: Claims 21-29, 31-32, and 36-37 (A copy of the claims on appeal, as amended, can be found in the attached Appendix.)

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, inter alia, to a polynucleotide encoding a polypeptide ("HSCOP-5") having homology to a SOCS protein, both the polynucleotide and the polypeptide having a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of HSCOP-5, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 39, line 29 through page 44, line 22 and page 45, line 22 through page 46, line 8).

As described in Table 2 and in the Specification at page 5, lines 29-30 and page 16, lines 3-8, HSCOP-5 contains regions with homology to WD-40 repeats at L166-D199, L210-N242, L252-D284, contains a region with homology to a SOCS box at V384-I421, and is homologous to WSB-1. As described in Table 3 and in the Specification at page 5, line 31 through page 6, line 2 and page 16, lines 9-14, SEQ ID NO:14, which encodes HSCOP-5, is expressed in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues.

(6) ISSUES

1. Whether Claims 21-29, 31-32, and 36-37 directed to SOCS protein polypeptides and polynucleotides meet the utility requirement of 35 U.S.C. § 101.

2. Whether one of ordinary skill in the art would know how to use the polypeptides and polynucleotides of Claims 21-29, 31-32, and 36-37, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to the utility rejection.

3. Whether one of ordinary skill in the art would know how to make and use the polypeptide variants and polynucleotide variants of Claims 21, 23, 26, 27, 28, 31, 32, and 36, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

4. Whether the polypeptide variants and polynucleotide variants of Claims 21, 23, 26, 27, 28, 31, 32, and 36 meet the written description requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

This issue pertains to Claims 21-29, 31-32, and 36-37.

As to Issue 2

This issue pertains to Claims 21-29, 31-32, and 36-37.

As to Issue 3

This issue pertains to Claims 21, 23, 26, 27, 28, 31, 32, and 36.

As to Issue 4

This issue pertains to Claims 21, 23, 26, 27, 28, 31, 32, and 36.

(8) APPELLANTS' ARGUMENTS

Issue 1: Utility Rejection of Claims 21-29,31-32, and 36-37

Claims 21-29, 31-32, and 36-37 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The

rejection alleges in particular that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Office Action mailed February 21, 2003[1], page 5.) In particular the Examiner alleges that "[t]he claimed invention . . . is directed to a polypeptide with no known activity" and that "[a]lthough instant specification asserts that claimed polypeptide can be used for diagnosis, treatment, or prevention of cancer, immune and neurological disorders and infectious diseases, (page 15, lines 20-24), it does not disclose how is the claimed polypeptide and polynucleotide can be used in these disparate diseases." (Office Action mailed February 21, 2003, pages 5-7.) The Examiner further alleged that "the physiological relevance of the claimed nucleic acid or the encoded polypeptide must be disclosed, in order to meet the requirements under 35 U.S.C. §101." (Final Office Action, page 4.)

The rejection of Claims 21-29, 31-32, and 36-37 is improper, as the invention of those claims has a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a gene that is expressed in human uterine endometrium tissue, as well as the polypeptide encoded by the polynucleotide. The polypeptide is identified in the patent application as a human SOCS protein, abbreviated as HSCOP-5. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of SOCS proteins, which function in cell signaling (Specification, pages 1-3.) The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the claimed polypeptide is a member of the SOCS protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide, as well as the polynucleotide

[1] In the Final Office Action, the Examiner states that "Claims 21-29, 31-32, and 36-37 stand rejected under 35 U.S.C. § 101 for reasons of record set forth in the office action mailed on 21 February 2002, pages 5-8." (Final Office Action, page 3.) Appellants note that the Office Action was mailed on **February 21, 2003**, not February 21, 2002.

encoding the polypeptide, also have patentable utility, regardless of the actual function of the claimed polypeptide. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Appellants previously submitted (in unexecuted form on June 23, 2003 and in executed form on July 11, 2003) the Declaration of Dr. Tod Bedilion (hereinafter "the First Bedilion Declaration") and the Declaration of Mr. Lars Michael Furness (hereinafter "the Furness Declaration") describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The First Bedilion Declaration and the Furness Declaration demonstrate that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide and polypeptide are without merit.

The First Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on May 28, 1998] that cDNA microarrays that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity. (First Bedilion Declaration, ¶ 15.)

The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

Appellants further submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before the May 29, 1998 priority date of the instant application.

Appellants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");

2. the Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Second Bedilion Declaration");

3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4. ten (10) references published before the May 28, 1998 filing date of the priority Lal '104 application,:

a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)

b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)

c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

h) Acacia Biosciences Press Release (August 11, 1997) (Reference No. 8)

i) V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997) (Reference No. 9)

j) J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997) (Reference No. 10)

The Rockett Declaration, the Iyer Declaration, and the Second Bedilion Declaration, and the ten(10) references, as well as the previously submitted First Bedilion Declaration and the Furness Declaration, fully establish that, prior to the May 28, 1998 filing date of the priority Lal '104 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools --

to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;

with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;

expression analysis is useful, inter alia, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;
>
> failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and
>
> failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner contends that the claimed polynucleotide and claimed polypeptide cannot be useful without precise knowledge of their biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the First Bedilion, Furness, Rockett, Iyer, and Second Bedilion Declarations, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide and the claimed polypeptide in the absence of any knowledge as to the precise function of the claimed polypeptide. The uses of the claimed polynucleotide and claimed polypeptide in gene expression monitoring applications including toxicology testing are in fact independent of the precise function of the claimed polynucleotide and claimed polypeptide.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the priority Lal '104 application relating to the use of the SEQ ID NO:14 polynucleotide and SEQ ID NO:5 polypeptide for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that the gene expression monitoring results obtained using the SEQ ID NO:14 polynucleotide or the SEQ ID NO:5 polypeptide allegedly provide "no meaningful information" or are otherwise insufficient to constitute substantial, specific and credible utilities for the SEQ ID NO:14 polynucleotide and

SEQ ID NO:5 polypeptide. (Final Office Action, e.g., page 5 and 11.) Indeed, the Final Office Action fails to acknowledge, let alone address, the priority Lal '104 application disclosure that cDNA microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Lal '104 application at page 30, lines 31-36.)

Under the circumstances, Appellants are submitting with this Appeal Brief the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A - Q; the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with attached Exhibits A-E; the Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132; and ten references published before the May 28, 1998 priority date of the instant application. As we will show, the Rockett Declaration, the Iyer Declaration, the Second Bedilion Declaration, and the accompanying references show the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the claimed SEQ ID NO:14 polynucleotide and SEQ ID NO:5 polypeptide in gene expression monitoring applications are without merit.

The fact that the Rockett, Iyer, and Second Bedilion Declarations, along with the accompanying references, are being submitted in response to positions taken and arguments made for the first time in the Final Office Action, constitutes by itself "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations and references were not earlier submitted and should be admitted at this time. Appellants also note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable

> of serving any beneficial end"). *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a

showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Uses of the claimed polynucleotide and claimed polypeptide for diagnosis of conditions and disorders characterized by expression of HSCOP-5, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the previously submitted First Bedilion Declaration and Furness Declaration, as well as in the Rockett Declaration, Iyer Declaration, and Second Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The claimed polypeptide's membership in the SOCS protein family demonstrates utility

Because there is a substantial likelihood that the claimed HSCOP-5 is a member of the family of polypeptides known as SOCS proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:5 in the patent application and referred to as HSCOP-5 in that application. Appellants have demonstrated by more than reasonable probability that HSCOP-5 is a member of the SOCS protein family, and that the SOCS protein family includes polypeptides which function in cell signaling. HSCOP-5 contains a region with homology to a SOCS box from residue V384 through I421 and contains regions with homology to WD-40 repeats at L166-D199, L210-N242, and L252-D284, and has homology to WSB-1 (Table 2 and Specification, pages 1-3).

The Examiner must accept the Appellants' demonstration that the claimed polypeptide is a member of the SOCS protein family and that utility is proven by a reasonable probability

unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the SOCS protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the SOCS protein family, useful.

Though not necessary to demonstrate the utility of the claimed SEQ ID NO:5 polypeptide, Appellants respectfully direct the Board's attention to the enclosed paper by D. Vasiliauskas et al., "SWiP-1: novel SOCS box containing WD-protein regulated by signalling centres and by Shh during development", Mech. Dec. (1999) 82:79-84 (Reference No. 11). This post-filing reference describes the characterization of a chick protein, termed cSWiP-1, which integrates two signals originating from structures adjacent to the segmental mesoderm: a positive signal from the notochord and a negative signal from intermediate and/or lateral mesoderm. The human homolog of cSWiP-1 is also described, which has 100% amino acid sequence identity to SEQ ID NO:5. (Alignment, Reference No. 12.) This post-filing reference confirms Appellants' prior identification of HSCOP-5 as a member of the SOCS protein family involved in cell signaling.

B. The uses of HSCOP-5 and the polynucleotide encoding HSCOP-5 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the previously submitted First Bedilion Declaration and Furness Declaration, and in the accompanying Rockett Declaration, Iyer Declaration, and Second Bedilion Declaration. The claimed polynucleotide is a useful tool in cDNA microarrays used to perform gene expression analysis. The claimed polypeptide is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. That is sufficient to establish utility for the claimed polynucleotide and the claimed polypeptide encoded by the claimed polynucleotide.

The instant application (the Lal '232 application) is the National Stage of International Application No. PCT/US99/11497, filed May 25, 1999 in the name of Preeti Lal et al., and

published in English as WO 99/61614 on December 2, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional applications U.S. Ser . No. 60/087,104, filed May 28, 1998 in the name of Preeti Lal et al. (hereinafter the Lal '104 application) and U.S. Ser. No. 60/150,701, filed December 17, 1998 in the name of Preeti Lal et al. The provisional applications provide support for what is disclosed in the instant Lal '232 application. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. The SEQ ID NO:5 polypeptide is referred to as HSCOP-5 in the instant Lal '232 application and as SOCP-5 in the priority Lal '104 application.

In his First Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Lal '104 application on May 28, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, e.g., as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (First Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (First Bedilion Declaration, ¶¶ 12 and 15).[2]

In connection with his explanations, Dr. Bedilion states that the "Lal '104 application would have led a person skilled in the art on May 28, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, and infectious diseases to conclude that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the Lal '232 application SEQ ID NO:14 polynucleotide." (First Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on May 28, 1998] that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool than a cDNA microarray that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide in connection with conducting gene expression

[2] Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '104 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (First Bedilion Declaration, ¶ 16).

monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-May 28, 1998 publications showing the state of the art on May 28, 1998 (First Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include more than three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on May 28, 1998 (and for several years prior to May 28, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Lal '104 application clearly include using differential gene expression analyses in toxicity studies (First Bedilion Declaration, ¶ 10).

Thus, the First Bedilion Declaration establishes that persons skilled in the art reading the Lal '104 application at the time it was filed "would have wanted their cDNA microarray to have a [Lal '232 application SEQ ID NO:14 polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to May 28, 1998." (First Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '104 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1998 would have understood that any expressed polynucleotide is useful for a number of gene expression monitoring applications, e.g., in cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been

> sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.][3]

In his Second Declaration, Dr. Bedilion explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Second Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

In addition, Dr. Rockett explains in his Declaration that "there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, including variants such as chemical cross-linking subtraction, suppression-PCR subtractive hybridization and representational difference analysis; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting and (5) EST analysis." (Rockett Declaration, ¶ 7.)

Nowhere does the Patent Examiner address the fact that, as described on page 44, lines 10-22 and page 53, lines 1-21 of the instant application, the claimed polynucleotide can be used as a highly specific probe in, for example, cDNA microarrays – a probe that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotide. The claimed polynucleotide is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement.

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[3] "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

Raytheon v. Roper, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The First Bedilion Declaration shows that a number of pre-May 28, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '104 application was filed (First Bedilion Declaration ¶¶ 10-14; First Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, First Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (First Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see [First Bedilion] Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the Lal '104 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (July 1999) (Rockett Declaration, Exhibit C).

In a post-May 28, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay. (emphasis added)

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Aug. 1997) (Reference No. 13).

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, e.g., in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, e.g., in the presence or absence of a drug. By comparing a map of cells treated with a potential drug

candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Lal '104 application. . . , the Wilkins article, and other related pre-May 28, 1998 publications, persons skilled in the art on May 28, 1998 clearly would have understood the Lal '104 application to disclose the SEQ ID NO:5 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶ 10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:5 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, [Furness Declaration] Tab C, page 26).

C. The uses of nucleic acids coding for proteins expressed by humans and of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease are now "well-established"

The technologies made possible by expression profiling using polynucleotides and polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development,

testing and safety assessment. These technologies include toxicology testing, as described by Bedilion, Furness, Rockett, and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett, et. al., supra:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett Declaration, Exhibit C, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 14); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 15).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 16, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir

paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 17) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]
>
> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]
>
> The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 -100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are

used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns*, or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]

[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]

The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix" (which is different from nucleic acid microarrays), which is based upon the measurement of protein expression levels. The patent further describes use of nucleic acid microarrays to measure transcript expression levels, making clear that the utility of comparing multidimensional expression datasets equally applies to protein expression data and transcript expression data. Additionally describing use of nucleic acid microarrays, the '588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained.

The '588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

> The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]
>
> The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism. [col. 1]
>
> The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix. [col. 2]
>
> Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression

of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [cols. 2 - 3]

Furthermore, it is not necessary to know the identity of any of the responding genes. [col. 3]

[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [col. 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [col. 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [cols. 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . .

> . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [col. 8]
>
> The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [col. 8]
>
> Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [col. 9]
>
> The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (Reference No. 8), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Reference No. 9), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]

> The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]
>
> As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]
>
> The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

Therefore, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the Wall Street Journal, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. The Uncontested Fact That the Claimed Polynucleotide Encodes a Protein in the SOCS Protein Family Also Demonstrates Utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotide encodes for a protein having the sequence shown as SEQ ID NO:5 in the patent application and referred to as HSCOP-5 in that application. Appellants have demonstrated that HSCOP-5 is a member of the SOCS protein family, and that the SOCS protein family members function in cell signaling.

The Patent Examiner does not dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept Appellants' demonstration that the polypeptide encoded by the claimed invention is a member of the SOCS protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the SOCS protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the claimed polypeptide encoded by the claimed polynucleotide must be, like the other members of the SOCS protein family, useful.

E. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or

sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotide and claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. Page et al., in discussing the identification and assignment of candidate drug targets, state that "rapid identification and assignment of candidate targets and markers represents a huge challenge ... [t]he process of annotation is similarly aided by the quantity and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)" Page, M.J. et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999) (Reference No. 18, see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described supra.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific" or "substantial" utilities. (Final Office Action, e.g., pages 5 and 6.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role, Function, Or Activity Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's rejection of the claimed invention is in part based on the ground that, without information as to the precise "biological activity" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polynucleotide either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polypeptide either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity.

It may be that detailed information on biological function is necessary to satisfy the requirements for publication in some technical journals, but it are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the First Bedilion and Furness Declarations (at, e.g., First Bedilion Declaration ¶¶ 10 and 15, Furness Declaration ¶¶ 10-12), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function, role, or activity of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and

substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function, role, or activity for any claimed polynucleotide or polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological function, role, or activity of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the SOCS protein family, as well as in the family of expressed polypeptides, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the SOCS protein family and the family of expressed polypeptides to HSCOP-5. In the Office Action, the Patent Examiner takes the position that, unless Appellants can identify which particular biological function within the class of SOCS proteins is possessed by HSCOP-5, utility cannot be imputed. To demonstrate utility by membership in the class of SOCS proteins, the Examiner would require that all SOCS proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. E.g., *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses HSCOP-5 as if the general class in which it is included is not the SOCS protein family and the family of expressed polypeptides, but rather all polynucleotides or

all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the SOCS protein family and the family of expressed polypeptides do not. The SOCS protein family and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that HSCOP-5 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the SOCS protein family and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed HSCOP-5 polypeptide is useful. It follows that the claimed polynucleotide also is useful.

C. Because the uses of HSCOP-5 and a polynucleotide encoding HSCOP-5 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed polynucleotide or claimed polypeptide. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed polynucleotide or claimed polypeptide invention as a tool are not used merely to study the claimed polynucleotide and claimed polypeptide themselves, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (First Bedilion Declaration at ¶ 15, Furness Declaration at ¶ 12.)

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polypeptides and polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the **identity** of that polypeptide or polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide or polynucleotide in toxicology testing is specific to both the compound being tested and the polypeptide polynucleotide used in the test. **No two human-expressed polypeptides or polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides or polynucleotides will differ

depending on the identity of the compound tested and the **identities** of the two polypeptides or polynucleotides. It is not necessary to know the biological functions and disease associations of the polypeptides or polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotide and claimed polypeptide are specific controls for toxicology tests in developing drugs targeted to other polypeptides or polynucleotides, and are clearly useful as such.

As an example, any histone gene or protein expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene or protein may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene or protein is surely an excellent subject for toxicology studies when developing drugs targeted to other genes or proteins. A drug candidate which alters expression of a histone gene or protein is toxic because disruption of such a pervasively-expressed gene or protein would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene or protein, measuring the expression of a histone gene or protein is a good measure of the toxicity of that candidate, particularly in in vitro cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene or protein in toxicology testing is specific and substantial because a toxicology test using that histone gene or protein cannot be replaced by a toxicology test using a different gene, including any other histone gene or protein. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene or protein.

The expression of the SEQ ID NO:14 polynucleotide and SEQ ID NO:5 polypeptide in human tissues would lead a skilled artisan to believe that this polynucleotide and this polypeptide have some physiological implications, even if these implications have not been precisely identified. During toxicology testing, a change in expression of a human-expressed polynucleotide or expressed polypeptide indicates potential toxicity of a drug candidate, even if the physiological implications of that polynucleotide or of that polypeptide are unknown. Such a toxicology test allows one to choose a lead drug candidate which has minimal effects on the expression of proteins other than the protein to which the candidate is targeted. Such a lead drug candidate would be less likely to have unintended side effects than a drug candidate having greater effects on the expression of genes/proteins other than the intended drug target. Thus, the benefit of such a toxicology test is an increased chance of finding a safe and effective drug, and a corresponding reduction in the expense and time of bringing a drug to market.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses in chromosome mapping and drug screening (Specification, page 44, line 23 through page 46, line 8).

IV. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

The Examiner bases the utility rejection on two issues, that the utilities of the claimed polynucleotide in toxicology testing are "not specific to the claimed polynucleotides" and that "using the claimed nucleic acid in gene expression monitoring" would provide "no meaningful information" and that "significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue." (Final Office Action, pages 5 and 6.) The Examiner further alleged that "using the polypeptide of the instant invention for drug discovery, or for toxicology testing does not provide the claimed invention with specific or substantial utility, since any protein can be used for these general purposes." (Final Office Action, page 5.) Appellants demonstrate below that the claimed uses meet the requirement that the claimed invention yield a "specific benefit" and why these uses constitute more than "further research" into the claimed invention itself.

A. Biological function, differential expression, or disease association is irrelevant to utility

The Examiner states that "the asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue." (Final Office Action, page 6.) The Examiner further alleges that "the physiological relevance of the claimed nucleic acid or the encoded polypeptide must be disclosed ,in order to meet the requirements under 35 U.S.C. §101" and that "no meaningful information will be obtained form tracking the expression of the claimed nucleotide, because there is no physiological or biological significance attached to this nucleotide or the encoded protein." (Final Office Action, e.g., pages 4, 5, and 6.) The Examiner however continues to ignores other utilities discussed in the Specification and/or well known in the art, such as toxicology testing.

Appellants have demonstrated a utility for the claimed SEQ ID NO:14 polynucleotide and the encoded SEQ ID NO:5 polypeptide irrespective of whether or not a person would wish to perform additional experimentation on biological function, disease association, or differential expression as another utility. The fact that additional experimentation could be performed to determine the biological function, disease association, or differential expression of the claimed SEQ ID NO:14 polynucleotide and the encoded SEQ ID NO:5 polypeptide does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the biological function, disease association, or differential expression of the claimed SEQ ID NO:14 polynucleotide and the encoded SEQ ID NO:5 polypeptide. (See, e.g., Rockett Declaration, ¶ 18 and Iyer Declaration, ¶ 9.)

Monitoring the expression of the claimed polynucleotide or the claimed polypeptide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the biological function, disease association, or differential expression of the claimed polynucleotide or the claimed polypeptide. The claimed polynucleotide or the claimed polypeptide is useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotide or the claimed polypeptide.

B. Use of the claimed polynucleotide and claimed polypeptide in toxicology testing

The Final Office Action does not find the First Bedilion Declaration and Furness Declaration persuasive, alleging that "since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides" and that "without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay would mean." (Final Office Action, pages 6, 11, and 12.)

The Examiner's arguments amount to nothing more than the Examiner's disagreement with the First Bedilion Declaration and Furness Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' experts. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the First Bedilion Declaration and Furness Declaration demonstrate how one of skill in the art,

reading the specification at the time the priority Lal '104 application was filed (May 28, 1998), would have understood that specification to disclose the use of the claimed polynucleotide and claimed polypeptide in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the First Bedilion Declaration at, e.g., ¶¶ 10-16, Furness Declaration at, e.g., ¶ 10-12).

For example, monitoring the expression of the SEQ ID NO:14 polynucleotide and the SEQ ID NO:4 polypeptide is a method of testing the toxicology of drug candidates during the drug development process. Dr. Bedilion in his First Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets." (First Bedilion Declaration ¶ 10.) Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotide and the claimed polypeptide as requiring knowledge of either the biological function or disease association or differential expression of the claimed polynucleotide or claimed polypeptide. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotide or claimed polypeptide. The Examiner has refused to consider that the claimed polynucleotide or claimed polypeptide is useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotide or claimed polypeptide, but to other polynucleotides and polypeptides. This utility of the claimed polynucleotide or claimed polypeptide does not require any knowledge of the biological function or disease association or differential expression of the SEQ ID NO:14 polynucleotide or SEQ ID NO:5 polypeptide and is a specific, substantial and credible utility. (See, e.g., Rockett Declaration, ¶ 18 and Iyer Declaration, ¶ 9.)

The Final Office Action emphasizes that "since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides" (Final Office Action, page 12), however Appellants note that:

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966).

Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention.

C. Utility of all expressed polynucleotides and expressed polypeptides in toxicology testing

The Examiner argues that "[s]ince any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides." (Final Office Action, page 6 and 12.) The Examiner doesn't point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of expressed polynucleotides can be so used, then they all have utility. The issue is, once again, whether the claimed polynucleotide and claimed polypeptide have any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of well-established utilities PRESUPPOSES that many different inventions can have the exact same utility (if the Examiner's argument were correct, there could never be a well-established utility, because you could always find a generic group with the same utility!).

It is true that just about any expressed polynucleotide or expressed polypeptide will have use as a toxicology control, but Appellants need not argue this for the purposes of this case. Appellants argue only that this particular claimed invention could be so used, and has provided e.g., the First Bedilion Declaration, the Furness Declaration, the Rockett Declaration, and the Iyer Declaration to back this up. The point is not whether or not the claimed polynucleotide or claimed polypeptide is, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real-world, for real purposes.

Appellants note that monitoring the expression of the claimed polynucleotide is a method of testing the toxicology of drug candidates during the drug development process. If the

expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide (or its encoded polypeptide) is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from an array in a gene expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

D Appellants' Invention Has Specific Utility

The Examiner alleges that "since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides." (Final Office Action, pages 6 and 12.)

Appellants' submission of additional Declarations and references overcomes this concern. Those Declarations and references demonstrate that, far from applying regardless of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotide as a gene-specific probe depends upon specific properties of the polynucleotide, that is, its nucleic acid sequence.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, **binds specifically** and with minimal cross-hybridization, to the probe's cognate transcript" (Rockett Declaration, ¶ 10(i), emphasis added); "[e]ach gene included as a probe on a microarray provides **a signal that is specific to the cognate transcript**, at least to a first approximation." (Iyer Declaration, ¶ 7, emphasis added.)[4] Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling" (Rockett Declaration, ¶ 10(ii)); equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device." (Iyer Declaration, ¶ 7.)

[4] See Iyer Declaration, footnote at ¶ 7 for a slightly more "nuanced" view.

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30-40 years.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is specific to the subject matter claimed. This contrasts to general utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," i.e., unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is particular to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397,

and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, supra (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the sine qua non of utility; it is, at most, one of many factors to be considered.

As described supra, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. Supra § III.B. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefited the public, including the claimed invention. See supra § III.B. Thus the Training Materials cannot be applied consistently with the law.

Issue 2: Enablement Rejection of Claims 21-29, 31-32, and 36-37 with Respect to the Utility Rejection

The rejection set forth in the Final Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

Issue 3: Enablement Rejection of Claims 21, 23, 26, 27, 31, 32, and 36 with respect to polynucleotide variants and polypeptide variants

The Examiner further contended that "in the event that Applicants provide specific and substantial utility for the polypeptide of SEQ ID NO:5, instant specification would still fail to adequately describe and enable an isolated polypeptide comprising an amino acid that has at least 90% identity to the polypeptide of SEQ ID NO:5, as recited in claim 21 or an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14, as recited in claim 31." (Final Office Action, page 9.) The Examiner stated that "one of ordinary skill in the art would not know how to make or use all of the polypeptides and polynucleotides having 90% identity to SEQ ID NO:5 or SEQ ID NO:14, respectively, as encompassed by claims 21 and 31." (Final Office Action, page 10.) In particular the Examiner alleges that "it would be impossible to predict with certainty the effect of a substitution, insertion, or deletion of a series of nucleotides, or even one nucleotide, on the encoded product" and that "[w]ith respect to amino acid modifications, the instant specification does not provide the guidance to predictably alter by 10%, i.e. 42 amino acids in SEQ ID NO:5, with any reasonable expectation that the resulting protein will have the desirable biological activity." (Final Office Action, page 10.)

The claimed polynucleotides and polypeptides are enabled, i.e., they are supported by the Specification and what is well known in the art.

I. How to make

SEQ ID NO:5 and SEQ ID NO:14 are specifically disclosed in the application (see, for example, pages 5-6 and page 15 of the Sequence Listing). Variants of SEQ ID NO:5 and SEQ ID NO:14 are disclosed, for example, on page 14, line 27 through page 15, line 18, and on page 17, lines 3-21. Incyte clones in which the nucleic acids encoding the human HSCOP-5 were first identified and libraries from which those clones were isolated are disclosed, for example, in

Tables 1 and 4. Chemical and structural features of HSCOP-5 are disclosed, for example, in Table 2.

The Examiner alleged that "[t]o practice the instant invention . . . [would require] a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues of the disclosed polypeptide, which are required for functional and structural integrity of the claimed polypeptide or to determine all the possible polynucleotides comprising at least 90% identical to the polynucleotide of SEQ ID NO:14, which are encompassed by the claims." (Office Action mailed February 21, 2003, page 8.) However, Appellants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:5 and SEQ ID NO:14 and not by biological activity or "functional integrity." The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring" polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 40, line 24 through page 41, line 5) which can then be expressed to make polypeptide variants and how to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to the polynucleotide sequence of SEQ ID NO:14" scope and whether a given naturally occurring amino acid sequence falls within the "at least 90% identical to the amino acid sequence of SEQ ID NO:5" scope (e.g., page 11, lines 8-24, Example III at pages 48-49, and Table 5). In addition, determination of percent identity is well known in the art.

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 18, line 17 through page 19, line 22; page 20, line 8 through page 21, line 4; page 40, line 17 through page 41, line 13; and Example VI at page 52, lines 13-31. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:5, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:14. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain

variant polynucleotides of SEQ ID NO:14 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:5 recited by the present claims using conventional techniques of recombinant protein production.

The making of the claimed polynucleotide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 18, lines 11-16, page 21, lines 15-20, and page 21, line 29 through page 22, line 1. The making of the claimed polypeptide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 21, lines 15-20, page 22, lines 1-7, and page 22, line 13 through page 26, line 1.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

II. How to Use

The claimed polypeptide variants and polynucleotide variants are products of expressed genes. Therefore, these polynucleotide variants are useful for the same purposes as the polynucleotide comprising the polynucleotide sequence of SEQ ID NO:14 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 5. These polypeptide variants are useful for the same purposes as the polypeptide comprising the polypeptide sequence of SEQ ID NO:5. These utilities are described fully under the rejection under §101 (supra) of this Appeal Brief, in the previously submitted First Bedilion and Furness Declarations, and in the currently submitted Rockett, Iyer, and Second Bedilion Declarations. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner argues that "[w]ith respect to amino acid modifications, the instant specification does not provide the guidance to predictably alter by 10%, i.e. 42 amino acids in SEQ ID NO:5, with any reasonable expectation that the resulting protein will have the desirable biological activity." (Final Office Action, page 10.)

However, the Specification, along with what is well known to one of skill in the art, enable the use of the claimed polynucleotides and polypeptides in toxicology testing by virtue of their being expressed polynucleotides and polypeptides, regardless of their biological function or biological activity. The Examiner has confused use with biological function.

III. Summary

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Final Office Action has failed to provide any reasons why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides and polypeptides. Hence, a prima facie case for non-enablement has not been established with respect to the recited polynucleotides and polypeptides.

Issue 4: Written Description Rejection of Claims 21, 23, 26, 27, 31, 32, and 36

The Examiner alleged that "the structure of a polypeptide having at least 90% identity to SEQ ID NO:5, or an isolated polynucleotide comprising at least 90% identical to SEQ ID NO:14, has not been disclosed, in order to satisfy the written description provision of 35 U.S.C. 112, first paragraph." (Final Office Action, page 9.)

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics

> when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** (emphasis added, citations omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:5 and SEQ ID NO:14 are specifically disclosed in the application (see, for example, pages 5-6 and page 15 of the Sequence Listing). Variants of SEQ ID NO:5 and SEQ ID NO:14 are described, for example, at page 14, line 27 through page 15, line 18. In particular, the preferred SEQ ID NO:5 variants (at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to SEQ ID NO:5) are described, for example, at page 17, lines 3-6. In particular, SEQ ID NO:14 variants (at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to SEQ ID NO:14) are described, for example, at page 17, lines 14-19. Incyte clones in which the nucleic acids encoding the human HSCOP-5 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1 and 4. Chemical and structural features of HSCOP-5 are described, for example, in Table 2. Given SEQ ID NO:5, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:5 at least 90% identical to the amino acid sequence of SEQ ID NO:5. Given SEQ ID NO:14, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:14 at least 90% identical to the polynucleotide sequence of SEQ ID NO:14. The Specification describes (e.g., page 11, lines 8-24 and page 48, line 5 through page 49, line 20, and Table 5) how to use BLAST and other methods to determine whether a given sequence falls within the "at least 90% identical" scope.

There simply is no requirement that the claims recite particular variant polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants are defined in terms of SEQ ID NO:5 ("An isolated polypeptide selected from the group consisting of. . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5."). The polynucleotide variants are defined in terms of SEQ ID NO:14 ("An isolated polynucleotide selected from the group consisting of . . . b) a

polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:14.").

Because the recited polypeptide variants are defined in terms of SEQ ID NO:5, and the recited polynucleotide variants are defined in terms of SEQ ID NO:5 and SEQ ID NO:14, the precise chemical structure of every polypeptide variant and every polynucleotide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

I. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; i.e., "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 21 and 31 recites chemical structure to define the claimed genus:

21. An isolated polypeptide selected from the group consisting of. . .

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5. . .

31. An isolated polynucleotide selected from the group consisting of. . . :

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:14. . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5 and SEQ ID NO:14. In the present case, there is no reliance merely on a description of functional characteristics of

the polynucleotides and polypeptides recited by the claims. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Final Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

II. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078); Reference No. 19). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, inter alia, to SOCS proteins related to the amino acid sequence of SEQ ID NO:5. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as SOCS proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:5. The "variant language" of the present claims recites, for example, an isolated polypeptide "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5. . . " (note that SEQ ID NO:5 has 421 amino acid residues). This variation is far less than that of all potential SOCS proteins related to SEQ ID NO:5, i.e., those SOCS proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:5.

III. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 28, 1998. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:5 and SEQ ID NO:14, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and the claimed polynucleotide variants at the time of filing of this application.

IV. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5 and SEQ ID NO:14. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides and polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Final Office Action.

For at least the above reasons, Appellants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be overturned.

(9) CONCLUSION

Appellants request that the rejections of the claims on appeal be reversed for at least the above reasons.

Appellants respectfully submit that rejections for lack of utility based, inter alia, on an allegation of "lack of specificity," as set forth in the Final Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[5] to target rejections of claims to polypeptide and polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the Specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

[5] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

Respectfully submitted,
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Enclosures:

Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A - Q;

Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132;

Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E

Nineteen (19) references:

1. PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995)

2. PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)

3. M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (previously also submitted with the First Bedilion Declaration filed in unexecuted form on June 23, 2003 and in executed form on July 11, 2003)

4. PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (previously also submitted with the First Bedilion Declaration filed in unexecuted form on June 23, 2003 and in executed form on July 11, 2003)

5. U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)

6. R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (previously also submitted with the First Bedilion Declaration filed in unexecuted form on June 23, 2003 and in executed form on July 11, 2003)

7. PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)

8. Acacia Biosciences Press Release (August 11, 1997)

9. V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997)

10. J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997)

11. Daniel Vasiliauskas et al., SWiP-1: novel SOCS box containing WD-protein regulated by signalling centres and by Shh during development, Mech. Dev. 82:79-84 (1999) (previously also submitted with the Response filed June 23, 2003)

12. Alignment of SEQ ID NO:5 with g4754060 (previously also submitted with the Response filed June 23, 2003)

13. D. A. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Natl. Acad. Sci. U.S.A. 94:8945-8947 (previously also submitted with the Response filed June 23, 2003)

14. E. F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (previously also submitted with the Response filed June 23, 2003)

15. S. Steiner and N. L. Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (previously also submitted with the Response filed June 23, 2003)

16. J. C. Rockett and D. J. Dix, Application of DNA arrays to toxicology, Environ. Health Perspec. 107:681-685 (1999) (previously also submitted with the Response filed June 23, 2003)

17. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (previously also submitted with the Response filed June 23, 2003)

18. M. J. Page et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999).

19. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA 95:6073-6078 (1998). (previously also submitted with the Response filed June 23, 2003)

APPENDIX - CLAIMS ON APPEAL

21. (As Once Amended) An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:5,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5, and

c) an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:5.

22. (As Once Amended) An isolated polypeptide of claim 21 comprising the amino acid sequence of SEQ ID NO:5.

23. An isolated polynucleotide encoding a polypeptide of claim 21.

24. An isolated polynucleotide encoding a polypeptide of claim 22.

25. (As Once Amended) An isolated polynucleotide of claim 24 comprising the polynucleotide sequence of SEQ ID NO:14.

26. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 23.

27. A cell transformed with a recombinant polynucleotide of claim 26.

28. A method of producing a polypeptide of claim 21, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 21, and

b) recovering the polypeptide so expressed.

29. (As Once Amended) A method of claim 28, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:5.

31. (As Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:14,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:14,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

32. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 31.

36. A composition comprising a polypeptide of claim 21 and a pharmaceutically acceptable excipient.

37. (As Once Amended) A composition of claim 36, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:5.